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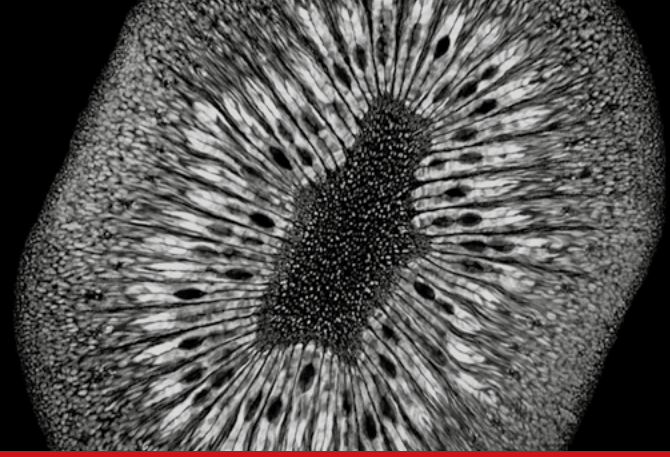
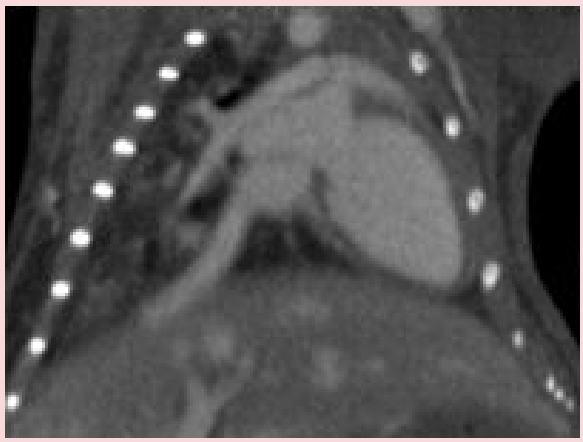


Left ventricular volume estimation



Left ventricular volume estimation using contrast-enhanced low-dose cone-beam µCT

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Introduction

Pre-clinical cardiac µCT of small rodents such as mice and rats is utilized, amongst others, for phenotyping, conducting therapeutic studies and studying animal models of heart disease. Especially in longitudinal studies, the radiation dose must be kept to an absolute minimum and yet, in order to obtain morphological and functional cardiac parameters, CT volumes with high spatial and temporal resolution are required. Owing to the high cardiac rate (about 600 beats/min) and rapid respiratory rate (about 300 breaths/min) of small animals, the scans need to be respiratory and cardiac gated[1,2]. It is a fact that conventional phase-correlated (PC) reconstruction of a given cardiac and respiratory phase utilizes only a small amount of the total data acquired (e.g., a respiratory window spanning 10 % of the respiratory cycle and a cardiac window of 10 % width imply that only 1 % of the projections are used for a PC reconstruction). As a result, unless the scans are acquired at a high radiation dose and a fine angular increment, resulting images are extremely noisy and estimated functional parameters, e.g. the end-diastolic left ventricular volume (EDV), are error-prone. We hereby propose a low-dose phase-correlated (LDPC) image reconstruction CT method that combines iterative reconstruction with 5D edge-preserving anisotropic filtering. Compared to conventional PC reconstruction, which is considered the gold standard, the proposed method can be performed at a radiation dose that is an order of magnitude less, thus, highly benefiting the animal under examination. Herein, we use contrast-enhanced µCT involving the innovative contrast agent ExiTron™ nano 12000 to compare PC and LDPC reconstruction methods for the estimation of cardiac parameters as exemplarily shown through measurement of the EDV.

Materials and methods

Cone-beam µCT scans were performed on healthy mice (n = 4) and each mouse was scanned 3 times, with repositioning between scans, resulting in 12 independent measurements (n = 12). Each scan comprised 7200 projections during 10 contiguous rotations within a period of 5 min at a low radiation dose of 250 mGy. The scans were used to perform both PC and LDPC reconstructions. Tail vein injection (6 mL/kg body weight) of the imaging agent, ExiTron™ nano 12000 (Viscover™, *nanoPET Pharma* GmbH, Berlin, Germany) resulted in marked contrast between the blood and the myocardium (~400 HU).

To correlate image reconstruction with the motion phases of the animal's heart and lungs, synchronization information was obtained directly from the raw data. This intrinsic gating

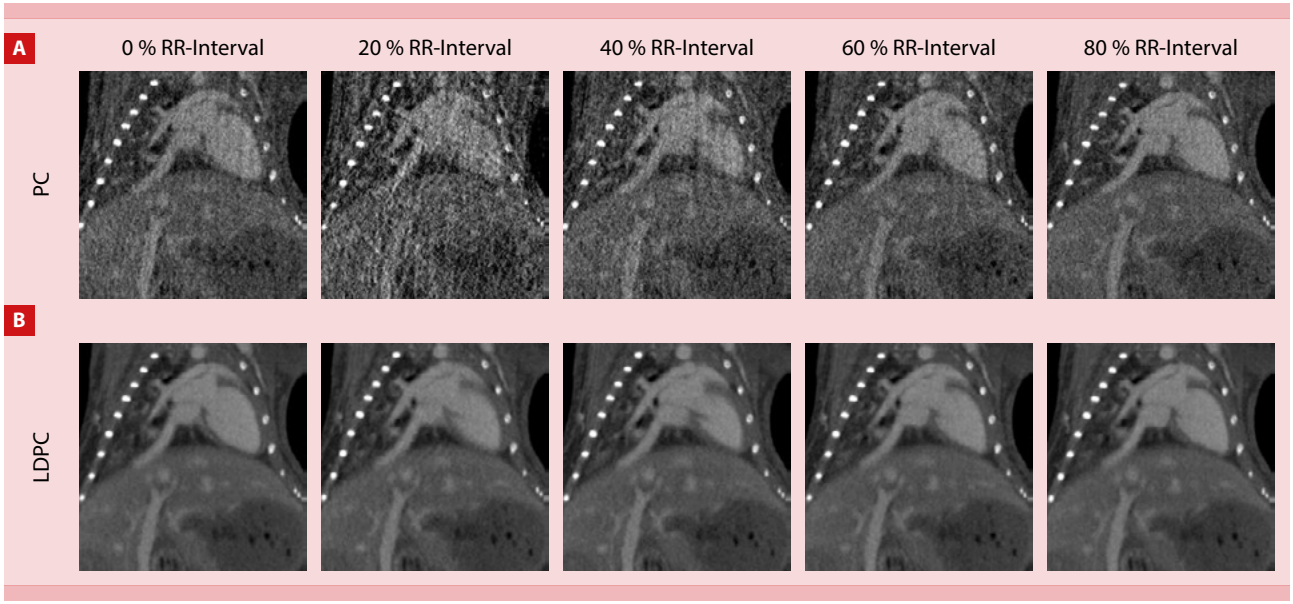

Figure 1: Coronal CT images at various time instants spaced equidistantly throughout the cardiac cycle acquired using the different reconstruction methods at a radiation dose of 250 mGy.
The **(A)** PC- and **(B)** LDPC-reconstructed images start in diastole during inhalation (far left) and are obtained after injection of ExiTron nano 12000, which provides marked contrast between the ventricular blood and the myocardium (~400 HU). Note the varying noise structure in the PC-reconstructed images, which is caused by the different number of projections contributing to each reconstruction (C/W = 300/700 HU).

technique was first developed for clinical cone-beam spiral CT scanners and thereafter adopted for µCT applications[3]. Since clinical scanners rotate up to 3 times during a single motion cycle, intrinsic gating in clinical CT is highly challenging. In the case of slowly rotating µCT scanners, however, a motion period is generally much shorter than the time needed for a full rotation and, thus, extraction of the synchronization signal may neglect the gantry rotation allowing relatively simple methods to be used for detection of the periodic motion.

Our standard PC reconstruction is based on a Feldkamp-like algorithm that processes only those projections that lie in the desired motion phase. Since only a few of the total acquired projections contribute to the reconstruction, the resulting volumes comprise a low signal-to-noise ratio and fine morphological details are lost in the noise. The standard McKinnon-Bates (MKB) algorithm[4] can be adapted to address these issues. First a prior image based on all acquired projections is reconstructed. This image is blurry in regions where motion takes place and is of high quality in all other regions. Thereafter, the prior image is forward-projected and the result is subtracted from the raw data. This subtracted data is then used for a PC reconstruction, which is added to the prior image. Since the respiratory motion dominates the cardiac motion, we extend the standard MKB method to a two-step algorithm, where we first apply MKB only to the respiratory signal and then use the respiratory-gated MKB image as a prior image for cardiac gating. Thereafter, we apply an edge-preserving, anisotropic de-noising filter in up to 5 dimensions (3 spatial and 2 temporal - respiratory and cardiac - dimensions). The final volumes obtained by MKB reconstruction and filtering are the LDPC volumes[5]. As a consequence of the extension of the MKB algorithm and filtering, our new LDPC method is computationally 5 times as demanding as standard PC reconstruction.

To estimate the EDV, a multi-level Otsu method[6] is applied to the data resulting in classification of tissues (blood, muscle and intermediate tissue). The EDV is estimated by summing the volumes of all voxels classified as blood in all volume slices. To provide a ground truth, reference EDV values were estimated by performing a high dose scan (1 Gy) for each mouse and thereafter analyzing the resulting images.

Results and discussion

To investigate the performance of the herein proposed LDPC reconstruction method in comparison to the standard PC method in estimation of cardiac parameters, healthy mice were injected with ExiTron nano 12000 and the resulting images were used for measurement of the EDV. Resulting CT images clearly show that the image quality using LDPC reconstruction is markedly superior to that obtained using PC reconstruction (Fig. 1). Indeed, using LDPC reconstruction, CT image noise was reduced by a factor of about 6 (from ~170 HU to ~30 HU) and this, using a low radiation dose of 250 mGy. In the literature[1], similar images (in terms of spatial resolution and image noise) are obtained at radiation doses that are far higher (more than ten-fold) than those employed using our LDPC approach[5]. Thus, compared to PC reconstruction, LDPC reconstruction enables high fidelity, low-dose, dual-gated imaging of free-breathing rodents without compromise in image quality.

Classification of the tissues enabled evaluation of the EDV in all tested mice (Fig. 2). PC reconstruction resulted in a mean EDV of 41 ± 16 µL, whereas estimation based on LDPC volumes resulted in a mean EDV of 48 ± 6 µL. The reference EDV was estimated at 48 ± 5 µL and highly corroborates published work[7]. The large deviations of the EDV estimated from the PC volumes originate from errors in the segmentation of the blood due to high noise and artifacts, as can be clearly observed in Fig. 2. This proves that, compared to the standard PC reconstruction method, the proposed LDPC method allows for accurate quantification of functional cardiac parameters with high fidelity at reduced radiation dose.

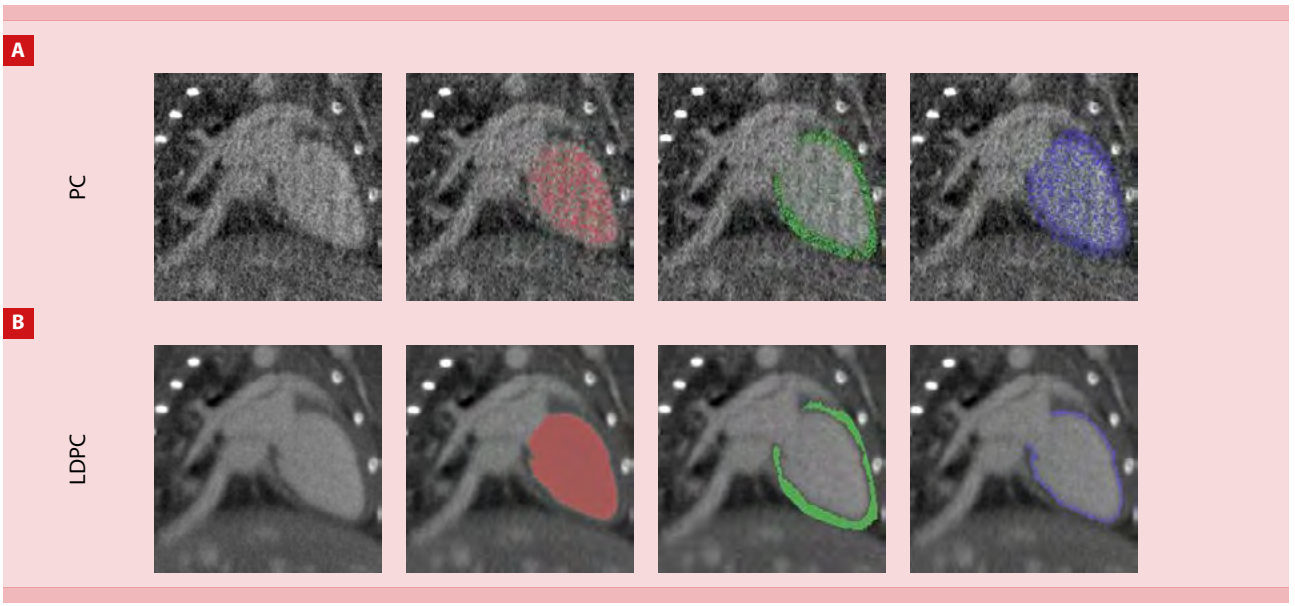

Figure 2: Classification of different tissue types namely blood (red), muscle (green), and intermediate tissue (blue) using **(A)** PC and **(B)** LDPC reconstructions (C/W = 300/700 HU).

Conclusion

In this study we developed a low-dose phase-correlated (LDPC) µCT method involving the use of ExiTron nano 12000 to effectively perform *in vivo* dual-gated CT imaging in free-breathing mice. Compared to conventional phase-correlated (PC) reconstruction, which is considered the gold standard, the new LDPC method uses a much lower radiation dose and yet results in highly improved CT images. The results show that the proposed LDPC method enables efficient evaluation of EDV values and, thus, accurate quantification of functional cardiac parameters. It, therefore, offers the possibility of performing longitudinal µCT studies while minimizing potentially adverse biological effects through ionizing radiation.

Acknowledgements

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